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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/383,978	08/26/1999	HEINZ SCHALLER	BBI-102CP	7239

28157 7590 01/15/2003

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	20

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/383,978	SCHALLER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2002 and 30 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8,33-36,39 and 41-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,33-36,39 and 41-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Due to the new ground of rejection summarized below, the finality of the Office Action mailed on 7/28/02 in Paper No. 17 is withdrawn.

Applicants' amendment filed on 12/04/02 in Paper No. 18 has not been entered because the clean copy of the amended claims does not match with the marked-up copy of the amended claims (specifically for claims 33 and 39). To correct this deficiency, Applicants submitted a supplemental amendment filed on 12/30/02.

Applicants' supplemental amendment filed on 12/30/02 in Paper No. 19 has been entered.

Amended claims 1, 4-8, 33-36, 39 and 41-50 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

Amended claims 33, 39 and 41 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing replication defective human hepatitis B virus and duck hepatitis B virus at a titer suitable for infecting hepatocytes in culture, wherein the S-gene in the genome of the hepatitis B virus has been replaced with a heterologous gene of up to 800 nucleotides in length such that expression of the heterologous gene is regulated by the S-promoter; and a replication defective hepadnavirus particle of the group consisting of human hepatitis B

virus and duck hepatitis B virus produced by the same method; does not reasonably provide enablement for a replication defective recombinant human hepatitis B virus and a recombinant duck hepatitis B virus containing a heterologous gene of any size, and a method for producing the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same ground of rejection set forth in the previous Office Action.

Amended claims 39 and 41 are directed to a method of producing replication defective hepadnavirus particles of human hepatitis B virus and duck hepatitis B virus at a titer suitable for infecting hepatocytes in culture comprising: co-transfecting hepatocyte cells of a hepatoma cell line with: (i) replication defective hepadnavirus constructs, wherein a region of one of an S-gene of the hepadnavirus DNA has been replaced with a gene encoding a heterologous gene, such that the expression of the heterologous gene is regulated by regulatory sequences of the S-gene; and (ii) a helper construct for transcomplementing lacking viral gene products; culturing the hepatocytes until infectious viral particles are produced; and recovering the infectious particles until infectious viral particles are produced; and recovering the infectious particles.

Amended claim 33 is directed to a replication defective hepadnavirus particle of the group consisting of human hepatitis B virus and duck hepatitis B virus, wherein a region of an S-gene of the hepadnavirus genome has been deleted and replaced by a heterologous gene such that the sequences that are essential for reverse transcription are retained.

The instant claims encompass the replacement of a region of the S-gene with a heterologous gene of any length. It is noted that the term a "region" of a gene refers to the length of nucleotide sequence of the hepadnavirus genome that is replaced by a heterologous gene not necessarily limited to any particular length (see instant specification, page 12, lines 8-13). The instant specification is not enabled for such a broadly claimed invention for the following reasons.

(a) The amount of direction or guidance presented. Apart from the exemplification showing the preparation of rDHBV-IFN, rDHBV-GFP and rHBV-GFP particles in which a heterologous gene encoding a green fluorescent protein or a duck type I interferon (less than 800 nucleotides) is substituted for the hepadnaviral S gene, the instant specification fails to provide sufficient guidance for a skilled artisan on how to generate suitable titers of replication defective recombinant hepadnavirus particles containing any heterologous gene larger than 800 nucleotides. For example, the specification fails to teach specifically which cis-acting control elements, internal promoters or enhancers and in which combinations should be maintained in order to achieve at least the titers obtained for the exemplified rDHBV and rHBV particles, and which additional hepadnaviral genomic segments to be deleted or replaced so as to increase the size of the heterologous gene.

(b) The state of the prior art and the unpredictability of the art. A hepatitis B virus (HBV) based vector is well known for its size constraint, particularly with respect to the infectivity of the recombinant hepadnaviruses. It is also known that the tiny hepadnaviral genome (3 kb) is virtually blanketed with critical cis-acting elements—

initiation sites for minus and plus strand DNA synthesis, promoter elements for multiple critical transcripts, and numerous sequences affecting RNA transport, processing, stability, and packaging (Ganem, Proc. Natl. Acad. Sci. 96:11696-11697, 1999; page 11696, col. 3, middle of the last paragraph; Cited previously). With the lack of sufficient guidance of the present disclosure on which cis-acting control elements, internal promoters or enhancers and in which combinations should be maintained, and which additional hepadnaviral genomic segments to be deleted or replaced so as to increase the size of the heterologous gene in order to achieve at least the suitable titers obtained for the exemplified rDHBV and rHBV particles, it would have required undue experimentation for a skilled artisan at the effective filing date of the present application to make and use the instant broadly claimed invention. Even a year after the effective filing date of the present application, Protzer et al. (Proc. Natl. Acad. Sci. 96:10818-10823; 1999; IDS) state "Despite these precautions (with respect to care taken not to exceed the authentic genome size an not to affect cis-acting control elements), among the several constructs in which different genome segments were replaced, **only substitution of the small envelope (S) gene by foreign sequences turned out to be successful**" (page 40820, col. 2, bottom of first paragraph).

(c) The relative skill of those in the art. Although the level of skill of an ordinary artisan in the art is high, given the fact that the tiny hepadnaviral genome (3 kb) is virtually blanketed with critical cis-acting elements—initiation sites for minus and plus strand DNA synthesis, promoter elements for multiple critical transcripts, and numerous sequences affecting RNA transport, processing, stability, packaging, and coupled with

the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan on a trial and error basis to make and use the instant broadly claimed invention.

(d) The breadth of the claims. The claims encompass the replacement of a region of the S-gene with a heterologous gene of any length. However, with the lack of sufficient guidance provided by the present disclosure and the state of the prior art as discussed above, it would have required undue experimentation for a skilled artisan to make and use the present broadly claimed invention. Additionally, the courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the aforementioned issues, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Examiner notes that Applicants failed to address the above issues in the Amendment filed on 12/30/02 in Paper No. 19.

Following is a new ground of rejection.

Claim R jections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Amended claims 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39 and its dependent claim recite the limitation "the gene encoding a cytokine" in line 8 of the claim 39. There is insufficient antecedent basis for this limitation in the claim. A gene encoding a heterologous gene is recited in the claim prior to this limitation. For the purpose of compact prosecution, Examiner interprets the claims as a method of producing replication defective hepadnavirus particles of human hepatitis B virus and duck hepatitis B virus containing a heterologous gene whose expression is regulated by regulatory sequences of the S-gene.

Additionally, in claim 39 the phrase "a gene encoding a heterologous gene" is unclear. How can a gene encoding another gene? Furthermore, the phrase "a region of one of an S-gene" is also unclear. Is there more than one S-gene in the hepadnaviral genome? Clarification is requested because the metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 102

Amended claims 1, 4-6, 33, 39, 41-45 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Horwich et al. (WO 90/02176; IDS).

Horwich et al. disclose the preparation of replication defective hepadnaviruses and in particular two types of defective hepadnavirus genomes, and the nucleic acid

sequences thereof (see abstract and pages 15-18). Horwich et al. disclose the first type ("particle defective" genomes) are incapable of supplying all hepadnaviral functions required for replication, but are able to produce a pregenome RNA with the appropriate cis-acting signals necessary for inclusion of the RNA in virions ("packaging") and for reverse transcription into DNA. The second type of defective hepadnavirus genomes ("packaging genomes") produced pre-genomic RNA which can not be packaged and/or reverse-transcribed into a double-stranded genomic DNA, and produce messenger RNAs capable of supplying functions required *in trans* for packaging. Horwich et al. further teach that hepadnavirus virion particles containing a particle-defective genome can be produced by coexpression of the particle-defective genome and "helper" hepadnavirus packaging genome(s). The resulting hepadnavirus containing a particle-defective genome can then be used for the infection of a hepatocyte, to which the particle-defective DNA is delivered and in which it can be expressed (page 16, second paragraph). Horwich et al. specifically teach to make permanent hepatic cell lines stably transfected with defective hepadnaviral genomes (packaging cell lines) that are capable of supplying necessary functions to defective hepadnaviral genomes and producing defective infectious particles (see page 18, first full paragraph). Horwich et al. teach the generation of several defective hepadnavirus genomes including those of hepatitis B virus pathogenic in humans, duck hepatitis B virus and others (see section 5.1.1 on page 29). Horwich et al. teach that their defective hepadnavirus virion particles containing a heterologous gene sequence which encodes for an immunogenic epitope (an agent that modulates a host immune response) or hepatic enzymes or a product

which is toxic to a given pathogen that is the causative agent of a disorder affecting the liver (see section 5.1.3.1 on page 38, and section 5.2 on page 44, particularly first full paragraph on page 45). Horwich et al. specifically teach that the heterologous gene sequence replaces the gene coding for the surface antigen, and specifically that the recombinant hepadnavirus DNA can retain pre-S DNA sequences which contain promoters for surface antigen expression (page 49, lines 1-5, and section 6.7 on page 69 for the exemplification showing the preparation of the S1 particle-defective genome by replacing the KpnI-XbaI fragment, 68 bp, located between nucleotide positions 1290 and 1358, of the DHBV wild-type sequence with a synthetic linker of the same size). Horwich et al. further teach that specific initiation signals are also required for efficient translation of inserted protein coding sequences. These signals include the ATG initiation codon and adjacent sequences. The initiation codon must be in phrase with the reading frame of the protein coding sequences to ensure the translation of the entire insert (see page 35, first full paragraph).

Therefore, the teachings of Horwich et al. meet every limitation of the instant claims. Accordingly, Horwich et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103

Claims 7, 8, 33-36, 42-43, 46-48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horwich et al. (WO 90/02176; IDS) in view of Alber et al. (U.S. Patent No. 5,928,636)

Horwich et al. disclose the preparation of replication defective hepadnaviruses and in particular two types of defective hepadnavirus genomes, and the nucleic acid sequences thereof (see abstract and pages 15-18). Horwich et al. disclose the first type ("particle defective" genomes) are incapable of supplying all hepadnaviral functions required for replication, but are able to produce a pregenome RNA with the appropriate cis-acting signals necessary for inclusion of the RNA in virions ("packaging") and for reverse transcription into DNA. The second type of defective hepadnavirus genomes ("packaging genomes") produced pre-genomic RNA which can not be packaged and/or reverse-transcribed into a double-stranded genomic DNA, and produce messenger RNAs capable of supplying functions required *in trans* for packaging. Horwich et al. further teach that hepadnavirus virion particles containing a particle-defective genome can be produced by coexpression of the particle-defective genome and "helper" hepadnavirus packaging genome(s). The resulting hepadnavirus containing a particle-defective genome can then be used for the infection of a hepatocyte, to which the particle-defective DNA is delivered and in which it can be expressed (page 16, second paragraph). Horwich et al. specifically teach to make permanent hepatic cell lines stably transfected with defective hepadnaviral genomes (packaging cell lines) that are capable of supplying necessary functions to defective hepadnaviral genomes and producing defective infectious particles (see page 18, first full paragraph). Horwich et al. teach the generation of several defective hepadnavirus genomes including those of hepatitis B virus pathogenic in humans, duck hepatitis B virus and others (see section 5.1.1 on page 29). Horwich et al. teach that their defective hepadnavirus virion particles

containing a heterologous gene sequence which encodes for an immunogenic epitope (an agent that modulates a host immune response) or hepatic enzymes or a product which is toxic to a given pathogen that is the causative agent of a disorder affecting the liver (see section 5.1.3.1 on page 38, and section 5.2 on page 44, particularly first full paragraph on page 45). Horwich et al. specifically teach that the heterologous gene sequence replaces the gene coding for the surface antigen, and specifically that the recombinant hepadnavirus DNA can retain pre-S DNA sequences which contain promoters for surface antigen expression (page 49, lines 1-5, and section 6.7 on page 69 for the exemplification showing the preparation of the S1 particle-defective genome by replacing the KpnI-XbaI fragment, 68 bp, located between nucleotide positions 1290 and 1358, of the DHBV wild-type sequence with a synthetic linker of the same size). Horwich et al: further teach that specific initiation signals are also required for efficient translation of inserted protein coding sequences. These signals include the ATG initiation codon and adjacent sequences. The initiation codon must be in phrase with the reading frame of the protein coding sequences to ensure the translation of the entire insert (see page 35, first full paragraph).

Horwich et al. do not specifically teach the utilized heterologous gene encodes for a cytokine, a chemochine or any one of IFNalpha, IFNbeta, IFNgamma, TNFalpha, IL-18 or IL-12.

However, at the effective filing date of the present application, Alber et al. teach that IFNalpha has proven to be effective in the treatment of viral infections, e.g., both HBV and HCV infections (col. 2, lines 1-3). Alber et al. also teach that the combined

use of IFNalpha and IL-12 is useful for treating chronic infectious viral diseases including hepatitis B, hepatitis C, HIV and others due to the synergistic interaction of IFNalpha and IL-12 (see abstract). Alber et al. also note that interferon cDNAs and IL-12 cDNA are available in the prior art, and therefore interferons and IL-12 can be produced recombinantly (see col. 1, lines 59-67; col. 4, lines 18-25).

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the replication defective recombinant hepadnaviruses, and methods for expressing a heterologous gene in a hepatocyte, and for producing replication defective recombinant hepadnavirus particles taught by Horwich et al. by using a gene encoding IFNalpha or other interferons (e.g., IFNgamma) or IL-12 as the heterologous gene in light of the teachings of Alber et al.

One of ordinary skilled artisan would have been motivated to carry out the above modification to produce recombinant interferons or IL-12 in a hepatocyte expression system because interferons and IL-12 are useful for treating chronic liver infectious diseases such as hepatitis B and hepatitis C. Alternatively, one of ordinary skilled artisan would have been motivated to carry out the above modification to investigate the effectiveness of the modified replication defective recombinant hepadnavirus particles expressing IFNalpha or IFNgamma or IL-12 in an animal model of chronic liver infectious diseases.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to LIE, Zeta Adams, whose telephone number is (703) 305-3291.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER